P3.2-058

Improved Clinical and MRI Disease Activity Outcomes, Including Slowing of Brain Volume Loss, in Alemtuzumab-treated RRMS Patients: 8-Year Follow-up of CARE-MS II (TOPAZ Study)

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OBJECTIVE

- **To evaluate the efficacy and safety of alemtuzumab over 8 years in RRMS patients from the CARE-MS II core study who entered the CARE-MS extension and TOPAZ studies**

INTRODUCTION

- In the CARE-MS II study (NCT00548405), 2 courses of alemtuzumab demonstrated significantly greater improvements in clinical and MRI outcomes versus subcutaneous interferon beta-1a (SC IFNB-1a) over 2 years[1]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[1]
- Efficacy was maintained over an additional 5 years in 2 consecutive extension studies (CARE-MS extension [NCT00930553] and the ongoing TOPAZ study [NCT02255656]); 47% of patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT) after the initial 2 courses[2-4]

METHODS

- In CARE-MS II, patients with active RRMS and an inadequate response to prior therapy received either alemtuzumab 12 mg/day IV on 5 consecutive days at baseline and on 3 consecutive days 12 months later, or SC IFNB-1a 44 µg 3×/week[1]
- In the CARE-MS extension study, patients could receive additional alemtuzumab courses (12 mg/day on 3 consecutive days ≥12 months after the most recent course) as needed for relapse or MRI activity, or other licensed DMTs at the investigator's discretion[2]
- In TOPAZ, patients can receive additional alemtuzumab courses (12 mg/day on 3 consecutive days ≥12 months after the most recent course) or other DMT at any time point, both at the investigator's discretion (no criteria)[4]

RESULTS

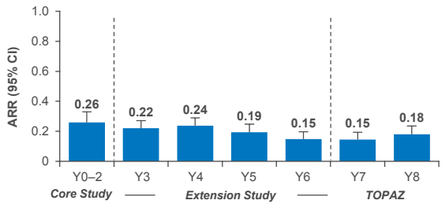
Patients and Additional Treatment

- Of the 435 patients who were treated with alemtuzumab 12 mg in CARE-MS II, 300 (69%) remained on study from core study baseline until the end of Year 8 (data cut-off date: October 4, 2017)
- Through Year 8, of the 393 patients who entered the extension study:
  - 172 (44%) received no additional treatment (no additional alemtuzumab courses and no other DMTs), 193 (49%) received no additional alemtuzumab treatment, and 343 (87%) received no other DMT
  - 115 (29%) received 1 additional alemtuzumab course, 63 (16%) received 2 additional courses, and 22 (6%) received >2 additional courses; 30 (8%) received alemtuzumab in Year 8
  - 50 (13%) received another DMT
- Reasons for receiving additional alemtuzumab were relapse (53%), MRI activity (18%), both relapse and MRI activity (21%), and other reasons/none provided (8%)
- Reasons for patient discontinuations in TOPAZ (Years 7–8; n=25 [6%]) were withdrawal of consent (n=6), study terminations by the sponsor at the patient's site (n=6), AE (n=5), physician decision (n=4), fatal event (n=1), and other reasons (n=3)

Clinical Efficacy

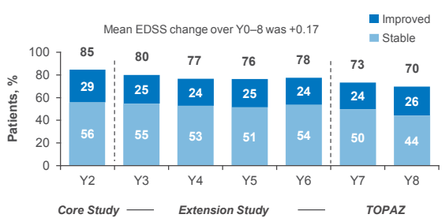
- Alemtuzumab-treated patients maintained a low annualized relapse rate (ARR) over 8 years (**Figure 1**), with a cumulative ARR (Years 3–8) of 0.19 (95% CI, 0.17–0.22)
  - 48% of patients were relapse-free in Years 3–8
- At Year 8, 70% of patients had improved or stable EDSS scores compared with core study baseline (**Figure 2**)
  - Mean EDSS change from core study baseline was +0.17

Figure 1. Relapse Rates Through Year 8



Y=year; ARR was estimated using a negative binomial model

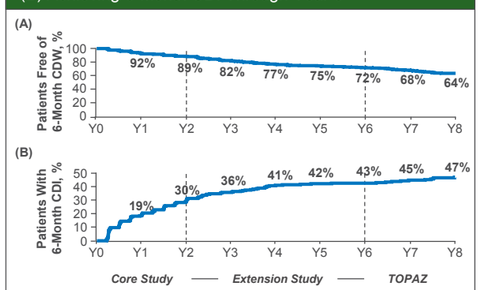
Figure 2. Improved or Stable EDSS Scores Through Year 8



Improved EDSS score: ≥1.0-point decrease from core study baseline; stable EDSS score: ≤0.5-point change in either direction from core study baseline; categories may not sum appropriately due to rounding

- Through Year 8, 64% of patients were free of 6-month confirmed disability worsening (CDW; **Figure 3A**), and 47% experienced 6-month confirmed disability improvement (CDI; **Figure 3B**)

Figure 3. Patients (A) Free of 6-Month CDW and (B) Achieving 6-Month CDI Through Year 8

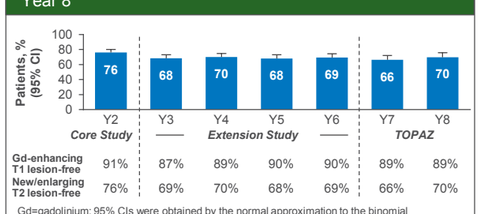


Kaplan-Meier estimates were used to assess proportions of patients with 6-month CDW and 6-month CDI; CDW: ≥1.0-point EDSS increase (or ≥1.5 points if baseline EDSS=0) confirmed over 6 months; CDI: ≥1.0-point EDSS decrease from baseline confirmed over 6 months (assessed only in patients with baseline EDSS score ≥2.0)

MRI Efficacy

- Over Years 3–8, 66%–70% of patients were free of MRI disease activity in each year (**Figure 4**)
  - Additionally, 86%–89% of patients had no new non-enhancing T1 hypointense lesions in each year over the same period
- Over Years 3–8, 53%–60% of patients achieved no evidence of disease activity (NEDA) in each year; 15% achieved NEDA sustained over Years 3–8

Figure 4. Freedom From MRI Disease Activity[a] Through Year 8



	Y2	Y3	Y4	Y5	Y6	Y7	Y8
Gd-enhancing T1 lesion-free	91%	87%	89%	90%	90%	89%	89%
New/enlarging T2 lesion-free	76%	69%	70%	68%	69%	66%	70%

Gd=gadolinium; 95% CIs were obtained by the normal approximation to the binomial distribution; [a]No new Gd-enhancing T1 lesions on current MRI or new/enlarging T2 hyperintense lesions since last MRI

References

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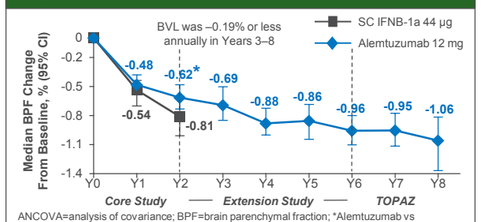
- Median percent cumulative brain volume loss (BVL) from core study baseline through Year 8 was –1.06% (**Figure 5**)
  - Over Years 3–8, BVL was –0.19% or less annually (Year 3: –0.10%; Year 4: –0.19%; Year 5: –0.07%; Year 6: –0.10%; Year 7: –0.16%; Year 8: –0.09%)

Figure 5. Reduction in BVL Over 8 Years



ANCOVA=analysis of covariance; BPF=brain parenchymal fraction; *Alemtuzumab vs SC IFNB-1a, *P*=0.0121 (based on ranked ANCOVA); Distribution-free estimates were obtained for the CI of the median; scans were read at the Cleveland Clinic (Cleveland, OH, USA) by assessors blinded to treatment

Please scan the QR code to see details on CARE-MS II safety through 8 years and additional information regarding safety in post-marketing use

Safety in Post-Marketing Use

- Through December 31, 2018, >24,000 patients have been treated worldwide with alemtuzumab for MS
- Post-marketing frequency (AEs and serious AEs [SAEs]) and clinical trial incidence (SAEs only) of key autoimmune events are presented in **Table 1**
- The post-marketing frequency of autoimmune AEs has generally been lower than expected based on the incidence observed in clinical trials
  - Compared with the clinical trial incidence, the post-marketing frequency of neutropenia was higher than the incidence of serious neutropenia events, but lower than the incidence including non-serious neutropenia (2-year incidence: alemtuzumab, 1.7%; SC IFNB-1a, 4%)[5]

Table 1. Key Autoimmune Events: Post-Marketing Frequency and Clinical Trial Incidence

Autoimmune Event	Post-Marketing Estimated Frequency (AEs/SAEs) (%)[a]	Clinical Trials SAEs Incidence (%)[5,b]
ITP	1.28	1.4
Hemolytic anemia	0.16	0.3
Pancytopenia	0.16	0.2
Nephropathies (including anti-GBM)	0.24	0.4
Neutropenia	0.93	0.2

GBM=glomerular basement membrane disease; ITP=immune thrombocytopenia; [a]Calculated as number of cases/total number of patients (n=24,062) treated through December 31, 2018; [b]Pooled CAMMS223, CARE-MS I and II, and CAMMS03409 data (cut-off date: February 2016), with median follow-up of 6.1 years (maximum 12 years)

- Labeling includes information regarding an increased frequency of infection and the potential for opportunistic infections (eg, varicella zoster, cytomegalovirus [CMV], tuberculosis, *Listeria monocytogenes*, superficial fungal infections, pneumonitis, and Epstein-Barr virus-associated lymphoproliferative disorders), acute acalculous cholecystitis, stroke, severe bleeding reactions, myocardial infarction and other cardiac disorders, autoimmune hepatitis, ITP, other autoimmune cytopenias, thyroid disorders, nephropathies (including anti-GBM disease), infusion-associated reactions, and other AEs following treatment with alemtuzumab
  - As anticipated, reports of opportunistic infections have been received in the post-marketing setting; the most commonly reported were *Listeria monocytogenes* (estimated frequency: 0.31%) and CMV (estimated frequency: 0.14%)
- In the post-marketing setting, cases of serious, sometimes fatal, stroke (hemorrhagic and ischemic) in patients receiving alemtuzumab for the treatment of relapsing MS have been reported
  - Some of these events occurred within 1 week of alemtuzumab administration; of these, most occurred within 1 day of infusion
  - The estimated frequency of stroke in patients treated with alemtuzumab is consistent with the incidence of stroke in the general population and lower than what has been reported in MS patients[6-9]
- There have been no reports of patterns or signals for malignancies

CONCLUSIONS

- **Efficacy of alemtuzumab on clinical, MRI lesion, and BVL outcomes was maintained over 8 years in patients with active RRMS who had an inadequate response to prior therapy**
  - **70% of patients had stable or improved disability based on EDSS scores through Year 8, and median cumulative BVL was –1.06% over 8 years**
  - **The robustness of these results is supported by the high retention rate (69%) from core study baseline, and is further underscored by the observation that 44% of patients received neither additional alemtuzumab courses nor other DMTs in the extensions through Year 8**
- **Over 8 years, the overall incidence of AEs decreased over time in patients who received alemtuzumab in CARE-MS II**

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

TOPAZ=a long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study

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P3.2-058 Supplemental Safety Information

Safety in the CARE-MS II Core and Extension Studies, and TOPAZ Study Through 8 Years

- The incidence of adverse events (AEs) in general was reduced in Years 3–8 compared with the core study (Years 1–2), and declined over time
  - The incidence of infections declined from Years 4–8; the incidence of serious infections was ≤3.3% per year through 8 years
  - Thyroid AE incidence peaked in Year 3, as reported previously,[2,4] and declined subsequently through Year 8; cumulative incidence in Years 1–8 was 43.7% for thyroid AEs and 5.1% for serious thyroid AEs
  - No immune thrombocytopenia (ITP) events occurred after the 48-month monitoring period following the last alemtuzumab dose; there were no new events in Year 8
  - No new autoimmune nephropathy cases occurred in Year 8
  - 10 malignancy cases were reported over 8 years: 2 thyroid cancers, 2 basal cell carcinomas, 2 malignant melanomas in situ, 1 B-cell lymphoma, 1 squamous cell carcinoma, and 1 breast cancer (all assessed by the sponsor as not related to alemtuzumab); 1 basal cell carcinoma (assessed by the sponsor as possibly related to alemtuzumab)
- In Year 6, 1 patient experienced cerebral hemorrhage and recovered
- The most commonly reported AEs were infusion-associated reactions (IARs), which declined after the first course of alemtuzumab (Course 1: 83.7%; Course 2: 71.5%; Course 3: 62.0%; Course 4: 64.7%)
  - The incidence of serious IARs was low (Course 1: 1.4%; Course 2: 1.4%; Course 3: 1.0%; Course 4: 1.2%)
- 6 deaths were reported in patients from CARE-MS II who entered TOPAZ (Years 7–8)
  - 2 deaths occurred in Year 7 and were reported previously (suicide [n=1], unknown cause [n=1; results of the autopsy were not provided]; assessed by both the sponsor and investigators as not related to alemtuzumab)[4]
  - 4 deaths were reported in Year 8, which were assessed by the sponsor and investigators as not related to alemtuzumab (sudden death [without autopsy], suicide, acute/organizing bronchopneumonia, and atrioventricular block, reported approximately 78, 30, 17, and 26 months after the last alemtuzumab dose, respectively)

Incidence of AEs by Year in the CARE-MS II Core and Extension Studies, and TOPAZ Study

	Incidence, %								Exposure-adjusted Incidence Rate Per 100 Patient-Years[a]		
	Y1 (n=435)[b]	Y2 (n=434)	Y3 (n=412)	Y4 (n=387)	Y5 (n=367)	Y6 (n=357)	Y7 (n=336)	Y8 (n=310)	Y0–2 (n=435)	Y3–8 (n=412)	Y0–8 (n=435)
Any AE	94.7	92.6	83.3	81.4	79.8	77.0	63.7	52.6	871.4	174.3	670.4
Serious AEs	12.6	9.9	10.2	14.5	10.4	9.0	9.2	7.7	11.1	9.1	8.9
Infections	63.2	61.8	50.0	50.6	44.7	44.0	35.7	28.4	89.0	43.1	56.5
Serious infections	2.1	1.8	1.2	2.3	1.9	1.7	3.3	1.3	1.9	1.7	1.6
Autoimmune AEs[c]											
Thyroid AEs	5.1	8.8	17.2	5.4	3.3	4.2	2.4	1.0	7.3	8.4	9.1
Serious thyroid AEs	0	0.5	3.2	1.3	0	0.3	0.3	0	0.2	1.0	0.8
ITP	0.2	0.7	0.2	1.8	0.3	0.6	0	0	0.5	0.5	0.5
Nephropathies	0	0.2	0	0	0	0	0.3	0	0.1	0	0.1
Malignancies	0	0.5	0.5	0	0	0.6	0.6	0.6	0.2	0.3	0.3

Y=year; [a]Exposure-adjusted incidence rate=(Number of patients with first AE in the time interval)/(Total follow-up duration [years] of all patients within the time interval, censoring at the time of AE for patients counted in the numerator) × 100; [b]Includes 9 CARE-MS II patients who received alemtuzumab 12 mg but who were originally randomized to receive alemtuzumab 24 mg; [c]First occurrence of AE for a patient

Additional Information Regarding Safety in Post-Marketing Use

- Post-marketing frequencies are not directly comparable to clinical trial incidences because of differences in ascertainment methodology and follow-up duration, and limitations of post-marketing reporting
  - Post-marketing reports may include non-serious cases, inaccurate diagnoses, and duplicate cases; most cases cannot be confirmed, the level of clinical detail available is often limited, and cases are subject to under-reporting
- The sponsor performs ongoing evaluation of post-marketing safety reports from multiple sources to refine understanding of the safety and benefit:risk profile of alemtuzumab and to identify potential new safety signals
- Engagement with health authorities occurs to ensure that alemtuzumab labels are updated to incorporate new information when clinically relevant:

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